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(54) Acetylcysteine compositions

(57) A pharmaceutical composition in the form of water-soluble effervescent granules or tablets comprises:

N-Acetylcysteine	6–32%
Citric acid	35–50%
Sodium bicarbonate	26–37%
Aspartame	1–1.5%
Flavouring agent	5–7%

The weight ratio of citric acid to sodium bicarbonate is from 1.2:1 to 1.4:1. The compositions have mucolytic activity, are non-cariogenic and are suitable for diabetics.

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SPECIFICATION

Pharmaceutical compositions

The invention relates to pharmaceutical compositions containing N-acetylcysteine.

N-acetylcysteine (hereinafter designated NAC) is a medicament with diverse favourable properties, one of which is mucolytic activity. For use in practice as a mucolytic agent, NAC can be taken orally in the form of an aqueous solution obtained by dissolving effervescent granules or an effervescent tablet. The organoleptic properties of the medicament can, however, be subjectively unpleasant. It is therefore necessary to lessen the typical taste of NAC in the case of oral administration.

In the pharmaceutical forms currently available commercially this is accomplished by an addition of sucrose. However, the use of sucrose can have disadvantages, especially for persons who suffer from diabetes. In addition, sucrose is a cariogenic sugar. It is therefore necessary to be able to provide, as an alternative to the already existing pharmaceutical forms, novel pharmaceutical preparations of NAC for oral use, which are indicated for subjects to whom sucrose can be harmful. The substitution of sucrose by an artificial sweetener or a non-cariogenic sweetening agent in a pharmaceutical form containing NAC is a problem which at first sight would appear easy to solve. In reality, there are manifold problems which are difficult to solve.

For example, it is necessary that the NAC and the sweetener are chemically compatible, that the sweetener or sweetening agent is capable of effectively masking or lessening the typical flavour of NAC, that the resulting taste is pleasant anyhow, that the sweetener or sweetening agent is suitable for preparing the desired pharmaceutical form and is compatible with the associated operations.

The invention provides a water-soluble effervescent pharmaceutical composition comprising from 6 to 32% by weight of N-acetylcysteine, from 35 to 50% by weight of citric acid, from 26 to 37% by weight of sodium bicarbonate, from 1 to 1.5% by weight of aspartame and from 5 to 7% by weight of a pharmaceutically acceptable flavouring agent, the weight ratio of citric acid to sodium bicarbonate being from 1.2:1 to 1.4:1.

The higher values for NAC correspond to the lower values for citric acid and bicarbonate. If desired, the citric acid can also be used partially in the form of a salt, for example as monosodium citrate.

The compositions according to the invention serve for preparing pharmaceutical forms as effervescent granules or tablets. Both the resulting pharmaceutical forms are readily soluble in water.

Having regard to the acceptability by the consumer of the medicament, the use of a flavouring agent may demand the presence of a colourant which is normally associated with a particular taste. For example, the use of mint flavouring can demand the addition of a colourant which imparts a green colour to the solution. In such cases, it can be useful to combine the composition with a quantity of a pharmaceutically acceptable colourant, for example in a quantity between 0.5 and 1% by weight.

Examples of compositions according to the invention are given in the Table which follows.

Table: Water-soluble effervescent compositions

	A		B		C		D		E		F		G	
	(mg)	(%)	(mg)	(%)	(mg)	(%)	(mg)	(%)	(mg)	(%)	(mg)	(%)	(mg)	(%)
NAC	100	10	200	20	100	6.67	150	10	200	13.33	400	23.53	600	31.58
Citric acid	470	47	412	41.2	738	49.20	708	47.20	680	45.34	680	40.00	680	35.79
Sodium Bicarbonate	345	34.5	303	30.3	542	36.13	522	34.80	500	33.33	500	29.41	500	26.32
Aspartame	15	1.5	15	1.5	20	1.33	20	1.33	20	1.33	20	1.18	20	1.05
Flavouring Agent	70	7	70	7	100	6.67	100	6.67	100	6.67	100	5.88	100	5.26
Total	1000	100	1000	100	1500	100	1500	100	1500	100	1700	100	1900	100

Amongst flavouring agents it is preferred to use lemon flavouring, the colour of the resulting solution being readily associated with the lemon taste. Alternatively, it is possible to use other agents, such as orange flavouring, which, however, is preferably combined with a suitable orange colourant, for example β-carotene.

By procedures usual in pharmaceuitcal operations, the compositions illustrated above may be prepared in the form of effervescent granules or tablets. Before packaging, the effervescent tablets are subjected to heating for a period of time determined as a function of the weight of the tablets. The granules are distributed in suitable sachets each containing from 1 to 2 g of the composition. Alternatively, tablets of a weight of 1, 1.2, 1.5, 1.7 or 1.9 g each are prepared.

If desired, for higher dosages of NAC (for example 600 mg per single dose), effervescent tablets of 3 g weight or sachets containing 3 g of effervescent composition can be prepared (see Example 5 below). A typical example of such a composition is as follows:

Composition H

	(mg)	(%)
NAC	600	20
Citric Acid	1211	40.36
$NaHCO_3$	1009	33.64
Aspartame	30	1
Citrus fruit flavouring	150	5
Total	3000	100

Both the effervescent granules and tablets according to the invention dissolve rapidly in water, giving an aqueous NAC solution of pleasant palatability.

The following Examples illustrate the invention.

Example 1

Granules consisting of

NAC	20	kg
Citric Acid	41.2	kg
Sodium bicarbonate	30.3	kg
Aspartame	1.5	kg
Lemon flavouring	7	kg

are prepared by the following procedure.

Granules consisting of NAC and citric acid are sieved through a screen of 1.07 mm mesh width and mixed after adding aspartame. The mixture is granulated with water in a fluid-bed granulator. Sodium bicarbonate and dried lemon flavouring are added to the granules obtained and mixed in. The mixture is distributed over blisters in a laminatedaluminium/polyethylene sheet in a dose of 1 g per blister.

Alternatively, aliquots of 1 g of the mixture can be compressed to tablets and be distributed over the blisters instead.

Example 2

Granules consisting of

NAC	60	kg
Citric acid	68	kg
Sodium bicarbonate	50	kg
Aspartame	2	kg
Orange flavouring	10	kg

are prepared by the following procedure.

NAC and citric acid are sieved through a screen of 1.07 mm mesh width and mixed after adding aspartame. The mixture is granulated in a fluid-bed granulator with an aqueous solution of colourant E110. Sodium bicarbonate and dried orange flavouring are added to the granules obtained and mixed in. Portions of 1.9 g of the mixture are then compressed in circular moulds of 18 mm diameter; giving effervescent tablets which each contain 600 mg of NAC. Before packaging in blisters, the tablets are heated on trays in a drying oven for 2 hours at 70°C.

Alternatively, the mixture can be distributed over blisters in a laminated aluminium/polyethylene sheet in a dose of 1.9 g per blister.

Effervescent granules or effervescent tablets of compositions corresponding to those described in the table given above are prepared by an analogous procedure.

Example 3

Granules consisting of:

NAC	40	kg
Citric acid	68	kg
Sodium bicarbonate	50	kg
Aspartame	2	kg
Citrus fruit flavouring	10	kg

are prepared by the procedure described in Example 1.

The dried mixture is then compressed in doses of 1.7 g each on a rotary tablet press fitted with moulds of 18 mm diameter. Alternatively, aliquots of 1.7 g are distributed over blisters in a laminated aluminium/polyethylene sheet. Both the tablets and blisters contain 400 mg of NAC per single dose.

Example 4

Granules consisting of:

NAC	10	kg
Citric acid	73.8	kg
Sodium bicarbonate	54.2	kg
Aspartame	2	kg
Orange flavouring	10	kg

are preparing by the following procedure.

NAC, citric acid and aspartame are sieved through a screen of 1.07 mm mesh width and mixed. The mixture is then granulated in a conventional granulator with an aqueous:alcoholic solution (water:alcohol = 1:1 by volume).

The granules obtained are dried in an oven and sieved on a vibrating granulator fitted with a screen of 0.9 mm mesh width. Sodium bicarbonate and orange flavouring are added to the granules obtained and mixed in.

Portions of 1.5 g of the mixture are then compressed in circular moulds of 15 mm diameter, forming effervescent tablets each containing 150 mg of NAC.

Alternatively, the effervescent mixture can be distributed over blisters in a laminated alumini-

um/polyethylene sheet in a dose of 3 g per blister, each containing 300 mg of NAC.

Example 5

Granules consisting of:

NAC	30 kg
Citric acid	60.55 kg
Sodium bicarbonate	50.45 kg
Aspartame	1.5 kg
Orange flavouring	7.5 kg

are prepared by the following procedure.

NAC and citric acid are sieved through a screen of 1.07 mm mesh width and mixed after adding aspartame. The mixture is then granulated with water in a conventional granulator. The granules obtained are dried in an oven and sieved in a vibrating granulator fitted with a screen of 0.9 mm mesh width. Sodium bicarbonate and orange flavouring are added to the granules obtained and mixed in.

Portions of 3 g of the mixture are then compressed in circular moulds of 25 mm diameter, forming effervescent tablets which each contain 600 mg of NAC.

Alternatively, the effervescent mixture can be distributed over blisters in a laminatedaluminium/polyethylene sheet in a dose of 3 g per blister, each containing 600 mg of NAC.

CLAIMS

1. A water-soluble effervescent pharmaceutical composition comprising from 6 to 32% by weight of N-acetylcysteine, from 35 to 50% by weight of citric acid, from 26 to 37% by weight of sodium bicarbonate, from 1 to 1.5% by weight of aspartame and from 5 to 7% by weight of a pharmaceutically acceptable flavouring agent, the weight ratio of citric acid to sodium bicarbonate being from 1.2:1 to 1.4:1.

2. A pharmaceutical composition according to Claim 1 in the form of effervescent granules.

3. A pharmceutical composition according to Claim 2 and containing a quantity selected from 150, 200, 300 400 and 600 mg of N-acetylcysteine per single dose.

4. A pharmaceutical composition according to Claim 1 in the form of effervescent tablets.

5. A pharmaceutical composition according to Claim 4 and containing a quantity selected from 150, 200, 300, 400 and 600 mg of N-acetylcysteine per single tablet.

6. A pharmaceutical composition according to any preceding Claim further comprising a pharmaceutically acceptable colourant.

7. A pharmaceutical composition according to any of Claims 1 to 5 and comprising:

N-Acetylcysteine	13.33% by weight
Citric acid	45.34% by weight
Sodium bicarbonate	33.33% by weight
Aspartame	1.40% by weight
Flavouring agent	6.60% by weight

8. A pharmaceutical composition according to any of Claims 1 to 5 and comprising:

N-Acetylcysteine	31.58% by weight
Citric acid	35.79% by weight
Sodium bicarbonate	26.32% by weight
Aspartame	1.05% by weight
Flavouring agent	5.26% by weight

9. A pharmaceutical composition according to Claim 7 and containing 200 mg of N-acetylcysteine per single dose.

10. A pharmaceutical composition according to Claim 8 and containing 600 mg of N-acetylcysteine per single dose.

11. A pharmaceutical composition according to any of Claims 1 to 5 and comprising:

N-Acetylcysteine	10% by weight
Citric acid	47% by weight
Sodium bicarbonate	34.5% by weight
Aspartame	1.5% by weight
Flavouring agent	7% by weight

12. A pharmaceutical composition according to any of Claims 1 to 5 and comprisig:

N-Acetylcysteine	20% by weight
Citric acid	41.2% by weight
Sodium bicarbonate	30.3% by weight
Aspartame	1.5% by weight
Flavouring agent	7% by weight

13. A pharmaceutical composition according to any of Claims 1 to 5 and comprising:

N-Acetylcysteine	10% by weight
Citric acid	47.20% by weight
Sodium bicarbonate	34.80% by weight
Aspartame	1.33% by weight
Flavouring agent	6.67% by weight

14. A pharmaceutical composition according to any of Claims 1 to 5 and comprising:

N-Actylcysteine	6.67% by weight
Citric Acid	49.20% by weight
Sodium bicarbonate	36.13% by weight
Aspartame	1.33% by weight
Flavouring agent	6.67% by weight

15. A pharmaceutical composition according to any of Claims 1 to 5 and comprising:

N-Acetylcysteine	23.53% by weight
Citric acid	40.00% by weight
Sodium bicarbonate	29.41% by weight
Aspartame	1.18% by weight
Flavouring agent	5.88% by weight

16. A pharmaceutical composition according to any of Claims 1 to 5 and comprising:

N-acetylcysteine	20% by weight
Citric acid	40.36% by weight
Sodium bicarbonate	33.64% by weight
Aspartame	1% by weight
Flavouring agent	5% by weight

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